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High-dose amino acid infusion preserves diuresis and improves nitrogen balance in non-oliguric acute renal failure

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Eine hohe Aminosäurenzufuhr erhält die Diurese und verbessert die Stickstoffbilanz bei nicht-oligurischem akuten Nierenversagen

Zusammenfassung. *Einleitung:* Der Einfluss einer Eiweiß-reichen Nahrung auf die glomeruläre Filtration ist sowohl beim Gesunden als auch beim chronisch nierenkranken Patienten gut belegt, beim akuten Nierenversagen bei kritisch kranken Patienten jedoch noch nicht untersucht worden. Die vorliegende Studie untersucht daher die Wirkung einer hohen Zufuhr von Aminosäuren auf die glomeruläre Filtrationsrate (GFR) und die N-Bilanz bei kritisch kranken Patienten mit akutem Nierenversagen.

Methoden: Vierzehn kritisch kranke Patienten mit einer Kreatinin-Clearance unter 50 ml/min und erhaltener Diurese über 2 000 ml/Tag erhielten 2000 nicht-Protein kcal und 75 g (Gruppe 1) oder 150 g (Gruppe 2) Aminosäuren parenteral pro Tag. Nierenfunktionsparameter, Flüssigkeitsbilanz, Na und N-Bilanz sowie der Bedarf an Furosemid wurden an den Tagen 2, 3 und 4 erhoben.

Ergebnisse: Die beiden Gruppen waren hinsichtlich Geschlecht, Schweregrad der Erkrankung, und Kreatinin-Clearance vergleichbar, Gruppe 2 allerdings signifikant ($p < 0{,}05$) älter. Der BUN stieg nur in der Gruppe 1 und nicht in der Gruppe 2 signifikant an. Die Kreatinin-Clearance blieb in beiden Gruppen unverändert. Gruppe 2 hatte eine signifikant positivere N-Bilanz (–10,5 ± 17 g/Tag 9 versus + 8,3 g/Tag) ($p < 0{,}01$), eine geringer positive Flüssigkeitsbilanz (2003 ± 1336 ml versus –2407 ± 1990 ml) und einen geringeren Furosemid-Bedarf (1003 ± 288 mg versus 649 ± 293 mg) ($p < 0{,}05$).

Schlussfolgerung: Die Gabe hoher Konzentrationen von Aminosäuren als Teil der parenteralen Ernährung verbessert die N-Bilanz, vermindert den Furosemid-Bedarf und führt zu einer günstigeren Flüssigkeitsbilanz bei Patienten mit nicht-oligurischem akuten Nierenversagen.

Summary. *Introduction:* The effects of protein-enriched diets on glomerular filtration have been described in normal subjects and in patients with chronic renal failure. In acute renal failure, the effects of administration of high rates of protein on renal function and nitrogen balance have not been studied in critically ill patients. The present study examines the effects of large doses of amino acids on the glomerular filtration rate and nitrogen balance in critically ill patients with acute renal failure.

Methods: Fourteen critically ill patients with a creatinine clearance below 50 ml/min and conserved diuresis above 2,000 ml/day received 2000 non-protein kcal/day and either 75 g (Group1) or 150 g (Group 2) of amino acids parenterally. Renal function tests, fluid balance, sodium and nitrogen balances, and furosemide administration were assessed on day 1 (baseline day when dextrose 5% was administered) and days 2, 3 and 4.

Results: The two groups were comparable in terms of severity indices, sex and creatinine clearance. Group 2 was significantly older ($p < 0.05$). Blood urea nitrogen increased significantly in Group 1 but not in Group 2; creatinine clearance remained unchanged in the two groups. Group 2 patients had a significantly more positive cumulative nitrogen balance (–10.5 ± 17 g/day vs. 9 ± 8.3 g/day) ($p < 0.01$), less positive fluid balance (2003 ± 1336 ml vs. –2407 ± 1990 ml) and lower furosemide requirement (1003 ± 288 mg vs. 649 ± 293 mg) ($p < 0.05$).

Conclusion: A high amino acid regimen administered as a part of parenteral nutrition improves nitrogen balance, reduces furosemide requirements and ameliorates water balance in acute renal failure patients with conserved diuresis.

Key words: Acute renal failure, high protein, parenteral nutrition, furosemide.

Introduction

Acute renal failure (ARF) is a frequent and severe complication in critically ill patients and is associated with high mortality [1, 2]. Oliguric ARF was an independent risk factor for overall mortality in a multivariate regression analysis of 384 cases of ARF from 16 countries [3]. Some oliguric ARF can be treated early with diuretics and non-oliguric ARF is then obtained; this is easier to manage since it may decrease requirements for hemodialysis, although without clear advantage in terms of mortality rate [4]. Management of non-oliguric ARF may require large amounts of furosemide [5], but treatment with this diuretic is associated with side effects such as electrolyte imbalance, ototoxicity and dehydration [5]. Further, a recent meta-analysis showed that furosemide was not associated with any significant clinical benefits in the prevention or treatment of ARF in adults [6].

ARF is associated with metabolic derangement and protein catabolism; it does not appear to increase resting energy expenditure but proteolysis is evident and the recommended daily protein intake for patients with ARF varies from 0.55–1.8 g/kg per day depending on the patient‘s condition and treatment [7]. In patients with sepsis, clearance of intravenously infused amino acids is greatly increased, suggesting that higher infusion rates of amino acids may be necessary to raise amino acid concentrations [8].

Enteral feeding including whole proteins or semielemental diet, or of amino acids through parenteral nutrition, increases the glomerular filtration rate (GFR) and renal blood flow in animals and normal humans [9, 10], and improvement in GFR following an amino acid load has also been observed in moderate and chronic renal failure [11, 12]. A high amino acid load is known to increase renal perfusion and renal function in healthy volunteers, but the question of whether it can improve or preserve renal function in ARF remains unanswered. Animal studies [13] and human studies in patients with cirrhosis [14] answer this question only partially. The present study was undertaken in order to observe the effect of high loads of amino acids on nitrogen balance and solute diuresis in critically ill patients suffering from non-oliguric ARF.

Patients and methods

Patients with conserved diuresis but suffering from ARF were prospectively included in the study. ARF was defined as a 50% decrease in GFR, a doubling of serum creatinine or an increase of creatinine to 3.5 mg/dl. Creatinine clearance (CrC) was calculated using the following formula:

$$\frac{\text{Urinary creatinine (mg/ml)} \times \text{urine output (ml)}}{\text{Plasma creatinine (mg/ml)} \times 1440\ \text{(min)}} \times 1.73$$

Patients were included in the study if they were critically ill, on ventilation, required parenteral nutrition and had a CrC < 50 ml/min and furosemide-induced diuresis > 2000 ml/day. Patients were prospectively randomized into two groups after receiving dextrose 5% on the first day. They then received a regimen of 2000 kCal/day of non-protein calories (dextrose and Intralipid, Fresenius-Kabi, Germany) plus either 75 g/day of amino acids (Group 1, normal-dose amino acids) or 150 g/day (Group 2, high-dose amino acids) (Aminoplasmal 10%, B Braun, Germany).

Anthropometric parameters, simplified APACHE physiological scores (SAPS II), diagnosis and renal function tests including blood urea nitrogen (BUN), serum and urine creatinine and CrC, as well as daily sodium excretion, daily diuresis and water balance were noted. Nitrogen balance was calculated using Lee's formula [10]. Furosemide prescriptions were followed daily for four days. Outcome and need for hemodialysis were reported. Patients' weights were not measured because the procedure was not sufficiently precise.

Patients receiving dopamine or mannitol and patients in shock or hemodynamically unstable were excluded from the study.

Statistical analysis defined the necessary number of patients to include in the study. Student's *t*-test was used to compare the two groups and a multiple ANOVA tested variations between days. The ethics committee of the Rambam Medical Center approved the protocol.

Table 1. Patients' characteristics

Patient	Diagnosis	SAPS	Age	BUN	CrC	RR	Outcome
Group 1: 2000 kcal/day and 75 g protein/day (normal dose) for 3 days							
1.	Pancreatitis	16	36	30	33	Yes	Died
2.	MOF aortobifemoral bypass	9	65	65	19.5	No	Died
3.	Guillain-Barré MSSA sepsis	10	49	53	41	No	Discharged
4.	Urosepsis	17	72	43	6	No	Discharged
5.	Behcet rupture of aortic abdomen	11	78	27	32	No	Discharged
6.	ARF	14	78	27	32	No	Discharged
Group 2: 2000 kcal/day and 150 g protein/day (high dose) for 3 days							
1.	Intra-abdominal sepsis	15	86	59	50	No	Discharged
2.	previous gastrectomy MOF	14	73	76	25	Yes	Died
3.	Multiple trauma	8	80	50	33	No	Died
4.	Perinephric abscess	9	67	51	12	No	Discharged
5.	Pneumonia	17	73	34	44	no	Discharged
6.	Acute MI resection of small bowel	15	74	58	42	Yes	Died
7.	Bleeding ulcer recurrent laparotomy	17	70	42	31	No	Discharged
8.	Incarcerated hernia	14	70	51	27.7	No	Discharged

MOF multiorgan failure; *MSSA* methicillin sensitive Staphylococcus aureus; *ARF* acute respiratory failure; *MI* acute myocardial infarction; *CrC* creatinine clearance; *RR* renal replacement therapy.

Table 2. Renal function modifications during infusion of 75 g vs 150 g amino acids with 2000 non-protein kCal/day of total parenteral nutrition

Days	Group 1: Normal amino acid load				Group 2: High amino acid load			
	1	2	3	4	1	2	3	4
BUN	45.2	53.3*	67.3*	59.0*	52.6	67.3	71.0	64.3
SD	14.7	8.9	21.2	5.1	12.5	9.6	10.8	6.4
Cr	1.9	2.0	1.9	2.5	2.3	1.8	1.9	1.9
SD	0.4	0.6	0.5	0.7	0.8	0.7	0.8	0.6
CrC	25.5	20.6	25.0	24.0	33.1	41.1	41.5	36.3
SD	12.7	8.6	14.8	16.6	12.2	16.6	22.0	13.3
Sodium output	457	328	399	331	583	536	540	639
SD	169	101	131	91	248	114	138	287
Furosemide	605	765	815*	910	392	435	497	506
SD	274	346	325	403	284	364	400	324
Water balance	1278	946	135	922	–103	–2625	709	–491
SD	2290	1848	1285	706	641	1924	2850	598
Daily nitrogen balance	–7.5	2	–1.3	–8.1	–15.8	8.1**	7.9**	8.0**
SD	14.3	4.5	5.8	19	16.2	6.9	7.2	3.8

$^*p < 0.05$ from baseline. $^{**}p < 0.01$ from baseline. *BUN* blood urea nitrogen (mg/dl); *Cr* creatinine (mg/dl); *CrC* creatinine clearance (ml/min). Sodium excretion is expressed in mEq/day, furosemide in mg/day and water balance in ml/day. Results are expressed as mean standard deviation (SD) on days 1 (baseline), 2, 3 and 4.

Results

Fourteen patients were included in the study (Table 1) and were similar regarding severity of sickness (SAPS II 12.8 ± 3.3 in Group 1 vs. 13.6 ± 3.4 in Group 2). Group 2 patients (n = 8) were significantly older ($p < 0.05$; 55 ± 20 years in Group 1 vs. 74 ± 6 years in Group 2). The same renal impairment characterized the two groups (BUN 45.2 ± 14.7 mg/dl and CrC 25.4 ± 12.7 ml/min in Group 1 vs. 52.6 ± 12.5 mg/dl and 33.1 ± 12.2 ml/min in Group 2).

BUN increased significantly ($p < 0.04$) from baseline on days 2, 3 and 4 in Group 1 but not in Group 2; however, CrC was not modified significantly from baseline (Table 2 and Fig. 1).

Daily water excretion was always > 3000 ml/day in both groups during the four days of the study. Cumulative water balance on days 2, 3 and 4 was +2003 ± 1336 ml in Group 1 and –2407 ± 1990 ml in Group 2 (NS). Urinary sodium excretion was not significantly modified in either group and not different between the groups. However, daily amounts of furosemide necessary to reach this diuresis were significantly lower on day 3 in Group 2 and cumulative doses from days 2, 3 and 4 were significantly lower in these patients ($p < 0.001$, Table 3).

Daily nitrogen balance showed no significant difference from baseline in Group 1 (Table 2); in Group 2, significant increase in nitrogen balance was observed

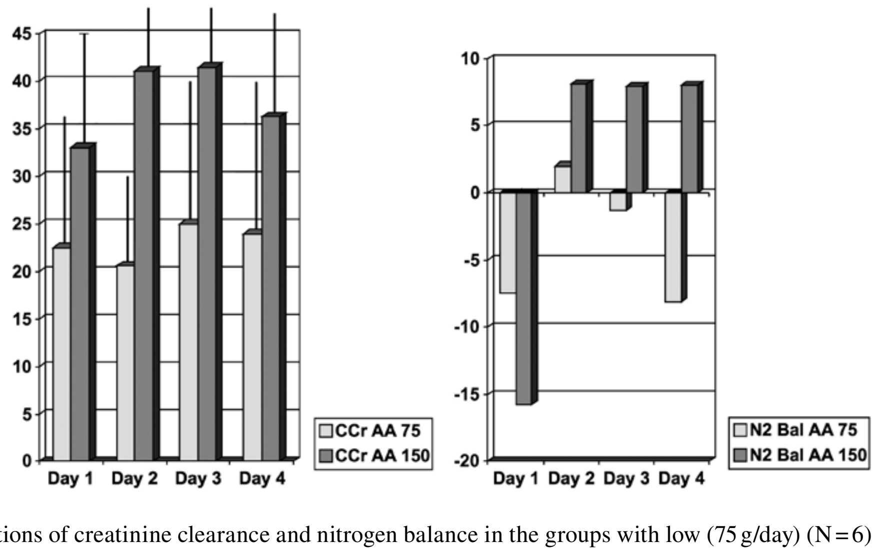

Fig. 1. Daily variations of creatinine clearance and nitrogen balance in the groups with low (75 g/day) (N = 6) and high (150 g/day) (N = 8) amino acid intake

Table 3. Mean daily furosemide use [mg/day] and nitrogen balance [g/day] on days 2, 3 and 4 in Group 1 receiving 75 g of protein and Group 2 receiving 150 g of protein. Both parameters are significantly different ($p < 0.001$)

	Group 1: Normal Amino Acids		Group 2: High Amino acids	
Furosemide ± SD	830	288	479	293
Nitrogen Balance ± SD	−10.5	17	2.9	8.3

from day 2 to day 4 ($p < 0.01$, Fig. 1), and when days 2, 3 and 4 were analyzed, cumulative nitrogen balance was significantly greater in this group (Table 3).

In Group 1, two out of six patients died and one required hemodialysis; in Group 2, three out of eight patients died and two required hemodialysis.

Discussion

Our results show that a high dose of amino acids (150 g/day), together with 2000 non-protein kcal/day, improves nitrogen balance in patients with non-oliguric ARF when compared with patients receiving the same number of calories but only 75 g/day of protein. It has been shown that administration of essential amino acids in association with dextrose decreased mortality in ARF [12, 13]; however, recommendations for calorie and protein administration in ARF are usually not for high amounts, to avoid fluid overload and increase in BUN [6]. Nevertheless, although increased resting energy expenditure is not often encountered, hypercatabolism is frequently observed in these patients [14] and maintenance of nitrogen balance is one of the main therapeutic goals, together with intermittent or continuous renal replacement [17]. In our study, high amino acid intake improved nitrogen balance and also enhanced the effect of furosemide, allowing a decrease of the prescription dose of this diuretic and a decrease in water retention. However, renal function was not modified.

Normal volunteers show an increase in GFR a few hours after a protein load [9]. However, kidney donors 1–11 years after donation and patients with acute glomerulonephritis or chronic renal failure have reduced renal functional reserve with or without diminished filtration capacity [10]. The authors of the latter study proposed a hypothetic diagram using serum creatinine levels and baseline GFR to predict the renal functional reserve capacity in progressive renal disease. In ARF, although amino acids have been recognized as dramatically improving survival, the recommended amount was not more than 1.5 g/kg body weight per day, because increased BUN would require an increase in hemodialysis sessions. Patients in a study by Scheinkestel et al. [18] achieved a positive nitrogen balance when protein intake was >2.0 g/kg per day; patients with a protein intake <2.0 g/kg per day failed to reach a positive balance. In non-oliguric ARF, we observed that an amino acid load of 75 g per day (Group 1) did increase BUN. The CrC was not modified in this group, and in Group 2 improved only from 31 ± 12 ml/min to 41 ± 13 ml/min (NS).

Moreover, the water balance was in favor of Group 2 (high doses of amino acids), despite the fact that they received 755 mg less (in absolute value) or 205 mg less furosemide than Group 1 when compared to baseline. Acute protein loading, in addition to increasing glomerular filtration in moderate renal failure also induces a predominantly proximal tubular response leading to increased excretion of sodium, creatinine and uric acid [19]. This phenomenon may explain the improvement in water balance observed in the group receiving the high amino acid load.

The limitations of the study should be considered: the size of the study group was small and the difference in age between the two groups may have influenced the results. No clear increase in GFR was noted.

We conclude that in non-oliguric ARF requiring large amounts of furosemide for conserved diuresis, high rates of amino acids infusion may not increase BUN more than a moderate dose, and may reduce furosemide requirements and improve nitrogen balance.

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